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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	1103326-0072
First Inventor	Per Lennart Lindberg
Title	New Compounds
Express Mail Label No.	EL286880185US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [X] Fee Transmittal Form (e.g., PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. [ ] Applicant claims small entity status. See 37 CFR 1.27.
3. [X] Specification [*Total Pages* 33] *(preferred arrangement set forth below)*
   - Descriptive title of the invention
   - Cross Reference to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
4. [ ] Drawing(s) *(35 U.S.C. 113)* [*Total Sheets*]
5. Oath or Declaration [*Total Pages* 3]
   a. [ ] Newly executed (original or copy)
   b. [X] Copy from a prior application (37 CFR 1.63 (d)) *(for continuation/divisional with Box 17 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. [ ] Application Data Sheet. See 37 CFR 1.76

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

7. [ ] CD-ROM or CD-R in duplicate, large table or Computer Program *(Appendix)*
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] paper
   c. [ ] Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. [ ] Assignment Papers (cover sheet & document(s))
10. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
11. [ ] English Translation Document *(if applicable)*
12. [X] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
13. [X] Preliminary Amendment
14. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [X] Other: SB/17; SB/22 - Petition for Extension of Time for 09/187,277

17. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:*

[XX] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No.: 09/187,277

Prior application information: Examiner J. Fan Group / Art Unit: 1625

For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

18. CORRESPONDENCE ADDRESS

[XX] *Customer Number or Bar Code Label* 007470 *(Insert Customer No. or Attach bar code label here)* or [ ] *Correspondence address below*

Name					
Address					
City		*State*		*Zip Code*	
Country		*Telephone*	212-819-8200	*Fax*	212-354-8113

Name (Print/Type)	John M. Genova	*Registration No. (Attorney/Agent)*	32,224
Signature	John M Genova	*Date*	Oct. 16, 2000

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FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT ($) 710

Complete if Known	
Application Number	TBA
Filing Date	TBA
First Named Inventor	Per Lennart Lindberg
Examiner Name	
Group Art Unit	
Attorney Docket No.	1103326-0072

METHOD OF PAYMENT

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:
   Deposit Account Number: 23-1703
   Deposit Account Name: White & Case
   [X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17
   [ ] Applicant claims small entity status. See 37 CFR 1.27
2. [X] **Payment Enclosed:** [X] Check [ ] Credit card [ ] Money Order [ ] Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	710	201	355	Utility filing fee	710
106	320	206	160	Design filing fee	
107	490	207	245	Plant filing fee	
108	710	208	355	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 710

2. EXTRA CLAIM FEES

		Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		X ---	=
Independent Claims	3	- 3** =		X ---	=
Multiple Dependent				---	=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	80	209	40	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	390	216	195	Extension for reply within second month	
117	890	217	445	Extension for reply within third month	890
118	1,390	218	695	Extension for reply within fourth month	
128	1,890	228	945	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,240	241	620	Petition to revive - unintentional	
142	1,240	242	620	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	600	244	300	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	710	246	355	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	710	249	355	For each additional invention to be examined (37 CFR § 1.129(b))	
179	710	279	355	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 890

SUBMITTED BY				Complete (if applicable)	
Name (Print/Type)	John M. Genova	Registration No. (Attorney/Agent)	32,224	Telephone	212-819-8200
Signature	John M Genova			Date	Oct. 16, 2000

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Date of Deposit *OCTOBER 16, 2000*.
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Iris Rivera
(Type or print name of person mailing paper or fee)

Iris Rivera
(Signature of person mailing paper or fee)

RE: Title: NEW COMPOUNDS
Inventor(s): Per Lennart Lindberg and Sverker Von Unge
Continuation application of USSN 09/187,277

The following are enclosed:

- Specification, claims, abstract - 33 pages;
- Copy of an executed Combined Declaration and Power of Attorney from prior related USSN 08/376,512;
- Preliminary Amendment;
- Information Disclosure Statement and PTO-1449 (no copies of references);
- PTO/SB/05 - Utility Patent Application Transmittal;
- PTO/SB/17 - Fee Transmittal;
- PTO/SB/22 - Petition for Extension of Time re prior related 09/187,277;
- Check $710 - filing fee; and
- Return postcard.

Respectfully submitted,

John M Genova

John M. Genova
Reg. No. 32,224

Customer Number 007470
(212) 819-8200
Attorney's Direct Line: (212)-819-8832

Enclosures

1103326-0072 CON3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Lindberg et al.
Serial No.	:
Filed	:
For	: NEW COMPOUNDS
Examiner	: J. Fan
Group Art Unit	: 1612

"Express Mail" Label No. EL286880185US
Date of Deposit Oct. 16, 2000

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Iris Rivera

Iris Rivera 10-16-00

Signature Date of Signature

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Applicants submit this Preliminary Amendment concurrently with their Request for Filing a Continuation Application pursuant to 37 C.F.R. §1.53(b). The new application is a continuation of pending U.S. Patent Application Serial No. 09/187,277, filed November 6, 1998, which is a

continuation of U.S. Patent Application Serial No. 08/899,931, filed July 24, 1997, abandoned, which is a continuation application of U.S. Patent Application Serial No. 08/376,512, filed January 23, 1995, now U.S. Patent No. 5,714,504, which is a continuation-in-part application of U.S. Patent Application Serial No. 08/256,174, filed June 28, 1994, now U.S. Patent No. 5,693,818.

IN THE SPECIFICATION:

Insert as the first sentence of the specification following the title, -- This is a continuation of pending U.S. Patent Application Serial No. 09/187,277, filed November 6, 1998, which is a continuation of U.S. Patent Application Serial No. 08/899,931, filed July 24, 1997, abandoned, which is a continuation application of U.S. Patent Application Serial No. 08/376,512, filed January 23, 1995, now U.S. Patent No. 5,714,504, which is a continuation-in-part application of U.S. Patent Application Serial No. 08/256,174, filed June 28, 1994, now U.S. Patent No. 5,693,818. --

IN THE CLAIMS:

Please amend the claims as follows:

Cancel claims 2-7, 10-18, 20, 23-34.

Amend claims 1, 8, 9, 19, 21 and 22 as follows:

1. (Amended) An optically pure [enantiomeric] compound comprising a magnesium [Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$] salt of [(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-H-benzimidazole or] (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-H-benzimidazole [, where R is an alkyl with 1-4 carbon atoms].

8. (Amended) The process according to claim 38, [7] wherein the diastereomers are separated by chromatography or fractional crystallization.

9. (Amended) The process according to claim 38, [7] wherein [the] solvolysis is performed in alkaline solution comprising [consisting of] a base in a protic solvent [comprising alcohol or water;] or a base in an aprotic solvent [, such as dimethylsulfoxide or dimethylformamide].

19. (Amended) A pharmaceutical composition comprising the [an] optically pure enantiomeric compound according to claim [the claims] 1 as active ingredient and a pharmaceutically acceptable carrier.

21. (Amended) A method for inhibiting gastric acid secretion comprising administration to a mammal [including man] in need of such treatment an effective amount of the [an] optically pure compound according to claim 1.

22. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal [including man] in need of such treatment an effective amount of the [an] optically pure compound or salt thereof according to claim 1 [claims 1 or 2].

Add new claims 35-42:

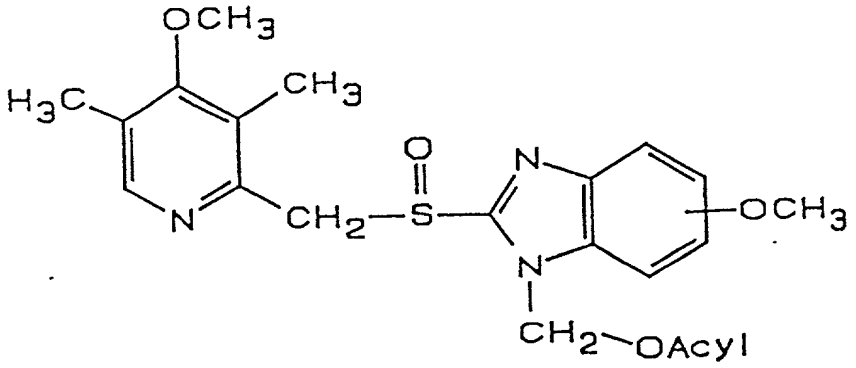
35. The compound according to claim 1 wherein the compound is in its crystalline form.

36. The compound 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole.

37. The compound 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole.

38. A process for the preparation of the optically pure compound according to claim 1 which comprises the steps:

(a) separating a diastereomeric mixture of an ester of formula IV



(IV)

to obtain the two diastereomers from the mixture, wherein Acyl designates a chiral acyl group having either R or S configuration;

(b) dissolving the diastereomer comprising the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole in an alkaline solution wherein the acyloxymethyl group is hydrolyzed off to give the to give the optically pure (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole; and

(c) converting the optically pure (-)-enantiomer to the magnesium salt.

39. The process according to claim 38, wherein the chiral acyl group is mandeloyl.

40. The process according to claim 9, wherein the protic solvent is selected from the group consisting of one or more alcohol and water, and wherein the aprotic solvent is dimethylsulfoxide or dimethylformamide.

41. The process according to claim 38, wherein the magnesium salt is obtained by treating the optically pure (-)-enantiomer with a base comprising magnesium in non-aqueous solution.

42. The process according to claim 38, wherein the magnesium salt of the optically pure (-)-enantiomer is obtained by first converting the optically pure (-)-enantiomer to a sodium salt and then treating the sodium salt with an aqueous solution of an inorganic magnesium salt to precipitate the magnesium salt of the optically pure (-)-enantiomer.

REMARKS

The new application is a continuation of pending U.S. Patent Application Serial No. 09/187,277, filed November 6, 1998, which is a continuation of U.S. Patent Application Serial No. 08/899,931, filed July 24, 1997, abandoned, which is a continuation application of U.S. Patent Application Serial No. 08/376,512, filed January 23, 1995, now U.S. Patent No. 5,714,504, which is a continuation-in-part application of U.S. Patent Application Serial No. 08/256,174, filed June 28, 1994, now U.S. Patent No. 5,693,818.

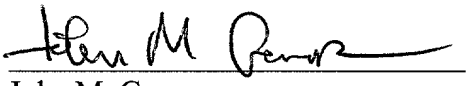
After entry of this Preliminary Amendment, the pending claims are original claims 1, 8, 9, 19, 21, 22 and 35-42. Applicants submit that the pending claims of this new continuation application correspond to the pending claims of the parent 09/187,277 application. Specifically, claims 1 and 35 of the new continuation application correspond to the examined claims 1 and 39 of the parent 09/187,277 application. Claims 8, 9, 19, 21, 22 and 36-42 of the new continuation application correspond to the claims which were withdrawn from consideration in the parent 09/187,277 application. Accordingly, no new matter has been introduced by any of the claim amendments or new claims.

Applicants respectfully submit that the claims are in condition for allowance, which action is earnestly solicited.

Any additional fees due in connection with Preliminary Amendment should be charged to Deposit Account No. 23-1703.

Dated: October 16, 2000

Respectfully submitted,



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NEW COMPOUNDS

This application is a continuation-in-part of copending Serial No. 08/256,174.

Field of the invention

The present invention is directed to new compounds of high optical purity and crystalline salts thereof, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

Background of the invention

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in United States Patent No. 4,255,431 to Junggren et al., EP 5129 and EP 124 495, respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers).

The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application (DE 4035455) this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because

there is a great risk of locally reaching pH values between 1-6, which would be devastating for the substance. Moreover, instantaneous neutralization will create heat which will be difficult to handle in large scale production.

There is no example in the known prior art of any isolated or characterized salt of optically pure omeprazole, i.e. of single enantiomers of omeprazole or of any isolated or characterized salt of any optically pure omeprazole analogue.

Summary of the invention

It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

A preferred embodiment of the present invention provides pure crystalline enantiomeric salts of omeprazole and methods for the preparation thereof.

A more preferred embodiment of the present invention is directed to an optically pure crystalline enantiomeric magnesium salt of omeprazole and method for the preparation thereof.

A nonaqueous process according to the present invention is directed to the preparation of crystalline forms of an optically pure enantiomer of omeprazole magnesium salt or analogues thereof which includes steps of stirring a crude preparation of the omeprazole enantiomer under nitrogen into a methanolic magnesium methoxide solution, precipitating inorganic magnesium salt with addition of a small amount of water, removing any precipitated inorganic magnesium salts, concentrating the residual methanolic solution, precipitating the

omeprazole enantiomer by adding acetone to the residual solution, and filtering off the optically pure enantiomer crystals of magnesium omeprazole or analogues thereof.

The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. This novel method can also be used in large scale to obtain single enantiomers of omeprazole in neutral form.

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned for treatment are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

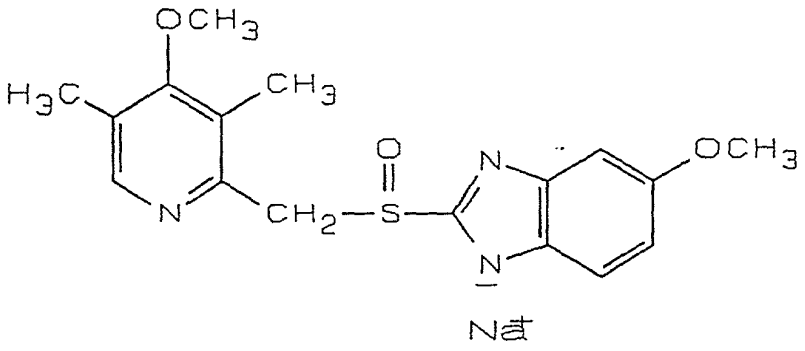
Detailed description of the invention

The present invention refers to the new Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of the single enantiomers of omeprazole, where R is an alkyl with 1-4 carbon atoms, i.e. Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and

(-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms.

Particularly preferred salts according to the invention are the Na^+, Ca^{2+} and Mg^{2+} salts, i.e (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt.

Most preferred salts according to the invention are the optically pure Na^+ salts of omeprazole according to compounds Ia and Ib

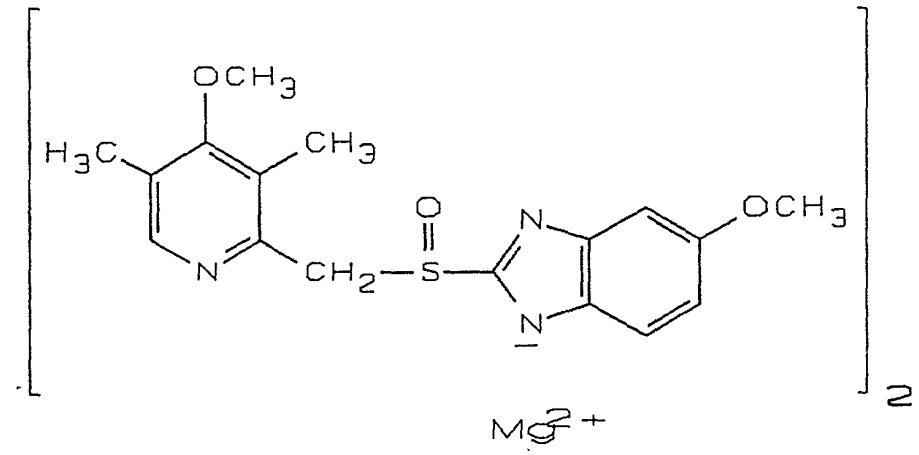


(Ia, Ib)

Ia (+)-enantiomer

Ib (-)-enantiomer

and the optically pure magnesium salts of omeprazole according to compounds IIa and IIb



(IIa, IIb)

IIa (+)-enantiomer

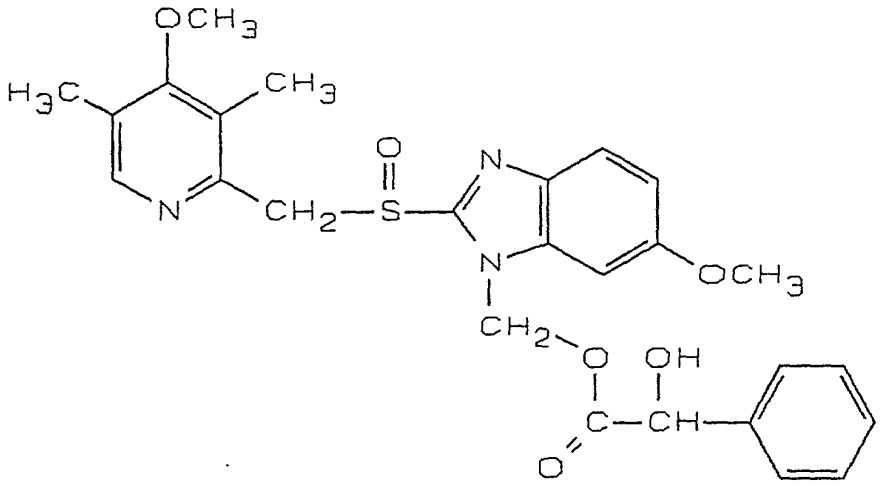
IIb (-)-enantiomer

With the expression "optically pure Na^+ salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (-)-enantiomer of omeprazole Na-salt and the (-)-enantiomer essentially free of the (+)-enantiomer, respectively. Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. The salts defined by the present invention are easy to obtain by means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole. In contrast to the neutral forms the salts can be obtained as crystalline products. Because it is possible to purify optically impure or partially pure salts of the enantiomers of omeprazole by crystallization, they can be obtained in very high optical purity, namely ≥99.8% enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high

stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy.

The specific method of preparation of the single enantiomers of omeprazole is a further aspect of the invention as mentioned above and it can be used to obtain the single enantiomers of omeprazole in neutral form as well as the salts thereof.

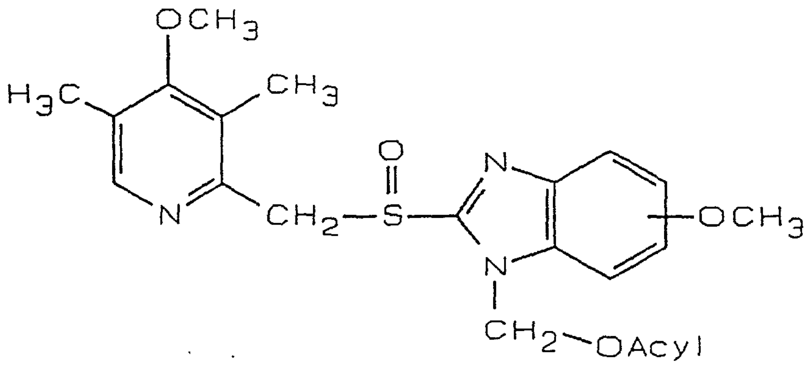
Yet a further aspect of the invention is the compound III, which is an intermediate used in the specific method of preparation.



(III)

Preparation

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV



(IV)

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

The diastereomeric esters can be separated either by chromatography or fractional crystallization.

The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water, but the acyl group may also be hydrolyzed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

To obtain the optically pure Na^+ salts of the invention, i.e. the single enantiomers of omeprazole Na^+ salts, the resulting compound is treated with a base, such as

NaOH, in an aqueous or nonaqueous medium, or with $NaOR^2$ wherein R^2 is an alkyl group containing 1-4 carbon atoms, or with $NaNH_2$. In addition, alkaline salts wherein the cation is Li^+ or K^+ may be prepared using lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

To obtain the optically pure Mg^{2+} salts of the invention, optically pure enantiomeric Na^+ salts may be treated with an aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomers of omeprazole with a base, such as $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds Ia and Ib) and the magnesium salts (compounds IIa and IIb), exemplified by their salts with Li^+, K^+, Ca^{2+} and $N^+(R)_4$, where R is an alkyl with 1-4 C-atoms.

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for

parenteral use and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These soultions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of

administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples using preferred procedures for the preparation of optically pure sodium salts and magnesium salts.

The processes described below for optically pure enantiomeric sodium salts of omeprazole result in change of directions from (-) to (+) optical rotation and, vice versa, from (+) to (-) optical rotation when preparing the sodium salt from the neutral form of omeprazole and again, when preparing the magnesium salt from the sodium salt of omeprazole.

Example 1. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was $\geq$99.8%. $[\alpha]_D^{20}$= +42,8° (concentration, c=0.5%, water).

NMR data are given below.

Example 2. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100mg-(0.3mmol)of(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (-)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 56 mg (51%) of the title compound as white crystals m.p. (decomposition) 247-249°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was ≥99.8%. $[\alpha]_D^{20}$= -44.1° (c=0.5%, water).

NMR data are given below.

Example 3. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

2.9 ml of a 0.1 M solution of NaOH was added to 0.10 g (0.29 mmol) (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. To this mixture 2 ml methylene chloride was added, and after mixing in a separatory funnel the aqueous solution was separated off. A solution of 14 mg (0.145 mmol) $MgCl_2$ in water was added dropwise. The formed precipitate was isolated by centrifugation, and 52 mg (50%) of the product was isolated as an amorphous powder. The optical purity (e.e.) was 98%, and thus the same as the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$= +101.2° (c=1%,

methanol). The Mg content of the sample was found to be 3.0%, shown by atomic absorption spectroscopy.

Example 4. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (0.500 g, 1.36 mmol) was dissolved in water (10 ml). To this mixture 10 ml of an aqueous solution of $MgCl_2xH_2O$ (138 mg, 0.68 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 418 mg (86%) of the product as a white powder. The optical purity (ee) of the product was 99.8% which was the same as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$= +129.9° (c=1%, methanol).

Example 5. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $MgCl_2xH_2O$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 85 mg (51%) of the product as a white powder. The optical purity (ee) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$= -128.2° (c=1%, methanol).

Table 1

Ex.	Solvent	NMR data δ ppm
1.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
2.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).

A preferred method for preparing optically pure omeprazole enantiomer crystal salts of magnesium is described in Examples 6 and 7.

Example 6. Enhancement of the optical purity by preparing the magnesium salt of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in nonaqueous solution followed by crystallization of said salt

Magnesium (0.11g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40°C with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(-)-isomer and 10%(+)-isomer] of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (2.84 g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (+)-isomer), with an optical purity

(enantiomeric excess, e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for 15 minutes, a white precipitate was obtained. Additional stirring for 15 mintues and thereafter filtration afforded 1.3 g (50%) of the title compound as white crystals. Chiral analyses of the crystals and mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the crystals and mother liquor was found to be 98.4 e.e. and 64.4% e.e., respectively. Thus, the optical purity (e.e.) has been enhanced from 80% to 98.4% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The product was crystalline as shown by powder X-ray diffraction and the magnesium content was 3.44% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20}$=-131.5° (c=0.5%, methanol).

Example 7. Enhancement of the optical purity by preparing the magnesium salt of (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in nonaqueous solution followed by crystallization of said salt

Magnesium (0.11 g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40°C with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(+)-isomer and 10%(-)-isomer] of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (2.84g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (-)-isomer), with an optical purity (e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for one hour, a white precipitate was obtained. Additonal stirring for 30 minutes and thereafter filtration afforded 0.35 g of the title

compound as white crystals. Additional stirring of the mother liquor for 24 hours at room temperature afforded another 1.0 g (total yield=52%). Chiral analyses of the crystals and the second mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the two crystal fractions was 98.8% e.e. and 99.5% e.e., respectively. The optical purity of the mother liquor was found to be 57% e.e. Thus, the optical purity (e.e.) has been enhanced from 80% to approximately 99% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The first precipitation was crystalline as shown by powder X-ray diffraction and the magnesium content of the same fraction was 3.49% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20}=+135.6°$ (c=0.5%, methanol).

The crystalline salt according to Example 6 is most preferred.

Preparation of the synthetic intermediates according to the invention is described in the following examples.

Example 8. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulfate and 6.4 g (42 mmol) (R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3 x 200 ml water and the organic solution was dried over $MgSO_4$ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

NMR data are given below.

Example 9. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1[(R) mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 8 were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5 % sodium hydrogen carbonate solution, drying over Na_2SO_4 and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colorless syrup.

NMR data are given below.

Example 10. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-

[chloromethyl]-1H-benzimidazole using the same procedure as in Example 8. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

NMR data are given below.

Example 11. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 10 were separated using reversed phase chromatography (HPLC) in the same way as in Example 7, but using the diasteromeric mixture of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 9. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colorless syrup.

NMR data are given below.

Example 12. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxide in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 μl (1.4 mmol)

methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.12 g (77%) of the title compound as a colorless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20}$= -155° (c=0.5%, chloroform).

NMR data are given below

Example 13. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxide in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and 25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 μl (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x25 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colorless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]_D^{20}$= +157° (c=0.5%, chloroform).

NMR data are given below

Table 2.

Ex.	Solvent	NMR data δ ppm
8.	$CDCl_3$ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
9.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
10.	$CDCl_3$ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
11.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).

12.	$CDCl_3$ 300 MHz	2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77 (m, 2H), 6.93 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.19 (s, 1H).
13.	$CDCl_3$	2.21 (s, 3H), 2.23 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.76 (m, 2H), 6.94 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.20 (s, 1H).

Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to Example 1	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavoring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavoring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound according to Example 6 as Mg salt	500 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Compound according to Example 6, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota^{R},

Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to Example 2	4 g
Sterile water to a final volume of	1000 ml

The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 μm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

Compound according to Example 6	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
Ethanol	600 g

The final coated pellets were filled into capsules.

Suppositories

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to Example 1	4 g
Witepsol H-15	180 g

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Stability towards racemization at different pH values

The stability of the optically pure compounds of the invention against racemization has been measured at low concentrations in a refrigerator in aqueous buffer

solutions at pH 8, 9.3, 10 and 11.2. The stereochemical stability was measured by comparing the optical purity for the (-)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several days. The measurement was performed by chromatography on an analytical chiral column. The surprising high stereochemical stability in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained at pH 11.2 even after 21 days. At pH 8, 9.3 and 10, the chemical degradation of the compound is more apparent which makes the racemization measurement more difficult to perform, however at none of these pH values a detectable racemization was obtained after 16 days.

In another racemization experiment with the optically pure compounds of the invention, an aqueous phosphate buffer solution (pH=11) of the (+)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt ($c=10^{-5}M$) was warmed for 26 hours at 37°C without any racemization at all being observed.

What is claimed is:

1. An optically pure enantiomeric compound comprising a Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-H-benzimidazole or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, wherein R is an alkyl with 1-4 carbon atoms.

2. The optically pure enantiomeric compound according to claim 1 selected from the group consisting of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt.

3. The optically pure enantiomeric compound according to claim 1 selected from the group consisting of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt.

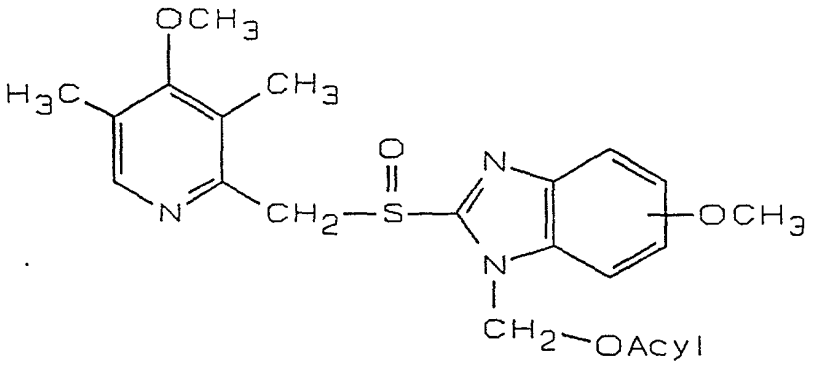
4. The optically pure enantiomeric compound according to claim 1 selected from the group consisting of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt and (-)-5-methoxy-2-[[(4-

methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole sodium salt in their crystalline forms.

5. The optically pure enantiomeric compound according to claim 1 which is (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt in its crystalline form.

6. The optically pure enantiomeric compound according to claim 1 which is the compound (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt in its crystalline form.

7. A process for the preparation of an optically pure enantiomeric compound according to claim 1 which comprises separating from a racemic mixture a diastereomeric ester of formula IV



(IV)

wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, and dissolving each of the separated R or S diastereomers is solved in an alkaline solution whereby the acyloxymethyl is hydrolyzed to give the optically pure enantiomeric compound.

8. The process according to claim 7 wherein the diastereomers are separated by chromatography or fractional crystallization.

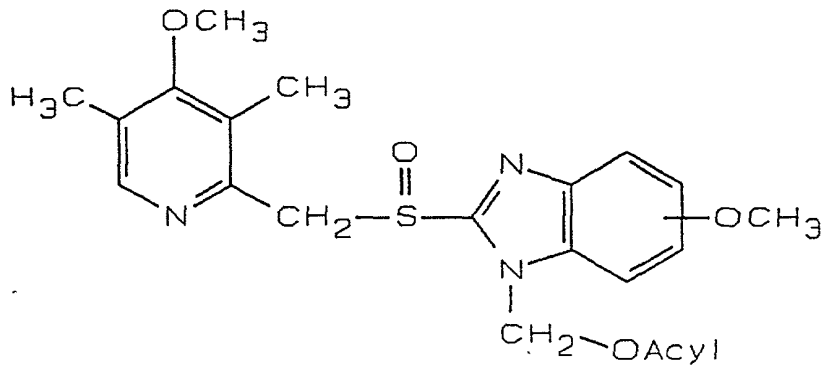
9. The process according to claim 7 wherein the solvolysis is performed in alkaline solution consisting of a base in a protic solvent comprising alcohol or water; or a base in an aprotic solvent, such as dimethylsulfoxide or dimethylformamide.

10. The process for the preparation of a pure enantiomeric compound according to claim 7 wherein a product from the process in crystalline form is neutralized with a neutralizing agent which can be an acid or an ester, followed by treatment with a base in non-aqueous solution.

11. A process for the preparation of crystalline sodium salt of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl-1H-benzimidazole sodium salt in crystalline form which comprises neutralizing (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt crude product or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole sodium salt crude product, respectively, is neutralized and treating said crude product with NaOH in a non-aqueous medium.

12. A process for the preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (-)-5-methoxy-2-[[(4-methoxy-

3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole which comprises separating a diastereomeric ester of formula IV



(IV)

wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration is and dissolving each of the separated diastereomers in an alkaline solution where the acyloxymethyl group is hydrolyzed off to give the optically pure enantiomeric compound after neutralization with a neutralizing agent which can be an acid or an ester.

13. The process according to claim 12 wherein the diastereomers are separated by chromatography or fractional crystallization.

14. The process according to claim 12 wherein the solvolysis is performed in alkaline solution consisting of a base in a protic solvent or of a base in an aprotic solvent.

15. The process according to claims 12 or 14 wherein the aprotic solvent comprises alcohol or water.

16. The process according to claims 12 or 14 wherein the aprotic solvent comprises dimethylsulforide or dimethylformamide.

17. The compound (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole obtained by the process defined in claim 12.

18. The compound (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole obtained by the process defined in claim 12.

19. A pharmaceutical composition comprising an optically pure enantiomeric compound according to the claims 1 as active ingredient and a pharmaceutically acceptable carrier.

20. An optically pure enantiomeric compound or salt thereof according to claims 1 or 2 for use in therapy.

21. A method for inhibiting gastric acid secretion comprising administration to a mammal including man in need of such treatment an effective amount of an optically pure compound according to claim 1.

22. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal including man in need of such treatment an effective amount of an optically pure compound or salt thereof according to claims 1 or 2.

23. The compound 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-1-[mandeloyloxymethyl]-1H-benzimidazole.

24. The optically pure enantiomeric compound according to claim 1 consisting of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium salt in its crystalline form.

25. The optically pure enantiomeric compound of claim 1 consisting of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt in its crystalline form.

26. The method of claim 21 wherein the optically pure enantiomeric compound is selected from the group consisting of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt.

27. The method of claim 21 wherein the selected optically pure enantiomeric compound is in crystalline form.

28. The method according to claim 22, wherein the optically pure enantiomeric compound is selected from the group consisting of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt.

29. The method according to claim 22 or claim 28 wherein the selected optically pure enantiomeric compound is in crystalline form.

30. An optically pure enantiomeric salt compound comprising the R or S diastereomeric structure of formula Ia, Ib, IIa or IIb, produced from a diastereomeric ester of formula IV, one diastereomer having been separated from

the other, dissolved in an alkaline solution and hydrolyzed therein resulting in the optically pure compound.

31. The compound according to claim 30 wherein one diastereomeric form is separated from the other by chromatography or fractional crystallization.

32. A nonaqueous process for preparing a crystalline form of an optically pure enantiomer of omeprazole magnesium salt which comprises stirring a crude preparation of the omeprazole enantiomer under nitrogen into a methanolic magnesium methoxide solution; precipitating any inorganic magnesium salts with a small addition of water; removing any precipitated inorganic magnesium salts; concentrating the residual methanolic solution; precipitating the omeprazole enantiomer by adding acetone; and filtering off the optically pure enantiomer crystals of magnesium omeprazole.

33. The process of claim 32, wherein the optically pure enantiomer is (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt or (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium crystal salt.

34. The process according to claim 7 or 12, wherein the chiral acyl group is mandeloyl.

Abstract

The novel optically pure compounds Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, in particular sodium and magnesium salt form thereof, where R is an alkyl with 1-4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.

White & Case
File No. 1103326-072

COMBINED DECLARATION
AND POWER OF ATTORNEY
(Original, Design, National Stage of PCT or CIP Application)

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NEW COMPOUNDS

the specification of which: (complete (a), (b) or (c) for type of application)

Regular or Design Application

(a) __ is attached hereto.
(b) X was filed on JANUARY 23, 1995 as Application Serial No. 08/376,512, and was amended on _____ (if applicable).

PCT Filed Application Entering National Stage

(c) __ was described and claimed in International Application No. _____ filed on _____ and amended on _____ (if any).

Acknowledgement of Review of Papers and Duty of Candor

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations § 1.56.

Priority Claim

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

(complete (d) or (e))

(d) __ no such applications have been filed.
(e) X such applications have been filed as follows:

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION

Country	Appl. No.	Date of Filing	Date of Issue	Priority Claimed
SWEDEN	9301830-7	28 MAY 1993		(X) Yes ( ) No
				( ) Yes ( ) No

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION

Country	Appl. No.	Date of Filing	Date of Issue	Priority Claimed
				( ) Yes ( ) No
				( ) Yes ( ) No
				( ) Yes ( ) No

Continuation-in-Part

(complete this part only if this is a continuation-in-part application)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior application and the national or PCT International filing date of this application:

08/256,174	28 JUN 1994	PENDING	
(Application Serial No.)	(Filing Date)	(Status)	(patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status)	(patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status)	(patented, pending, abandoned)

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File No. 1103326-072

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Date

Sverker von Unge
Signature of Inventor

Check proper box(es) for any added page(s) forming a part of this declaration

__/ Signature for subsequent joint inventors.
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__/ Signature by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor.
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__/ Signature for inventor who refuses to sign or cannot be reached by person authorized under 37 CFR 1.47.
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